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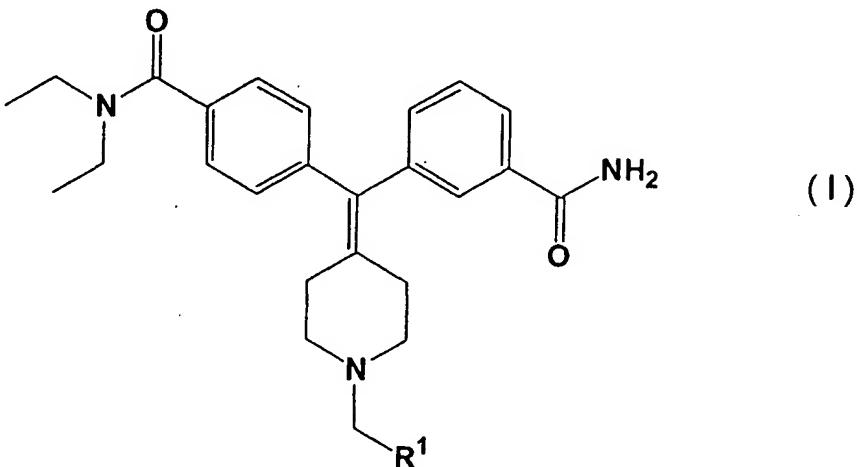
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(54) Title: 4[PIPERIDIN-4-YLIDEN-(3-CARBAMOYLPHENYL)METHYL] BENZAMIDE DERIVATIVES AND THEIR USE
FOR THE TREATMENT OF PAIN, SPINAL INJURIES OR GASTROINTESTINAL DISORDERS

WO 03/029215 A1

(57) Abstract: Compounds of general formula (I) wherein R¹ is selected from any one of phenyl, pyridinyl, thiényl, furanyl, imidazolyl, pyrrolyl and triazolyl; where each R¹ phenyl ring and R¹ heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents selected from straight and branched C₁-C₆ alkyl, NO₂, CF₃, C₁-C₆ alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on thephenyl ring and on the heteroaromatic ring may take place in any position on said ring systems; are disclosed and claimed in the present application, as well as their pharmaceutically acceptable salts and pharmaceutical compositions comprising the novel compounds and their use in therapy, inparticular in the management of pain.

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4[piperidin-4-yliden-(3-carbamoylphenyl)methyl] benzamide derivatives and their use for the treatment of pain, spinal injuries or gastrointestinal disorders

Field of the Invention

The present invention is directed to novel compounds, to a process for their preparation, 5 their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are useful in therapy, and in particular for the treatment of pain.

Background of the Invention

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as 10 analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ , δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal models when one or 15 more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. One example of a non-peptidic δ -agonist is SNC80 (*Bilsky E.J. et al., Journal of Pharmacology and Experimental Therapeutics, 273(1), pp. 359-366 (1995)*). There is however still a need for selective δ -agonists having not only improved 20 selectivity, but also an improved side-effect profile.

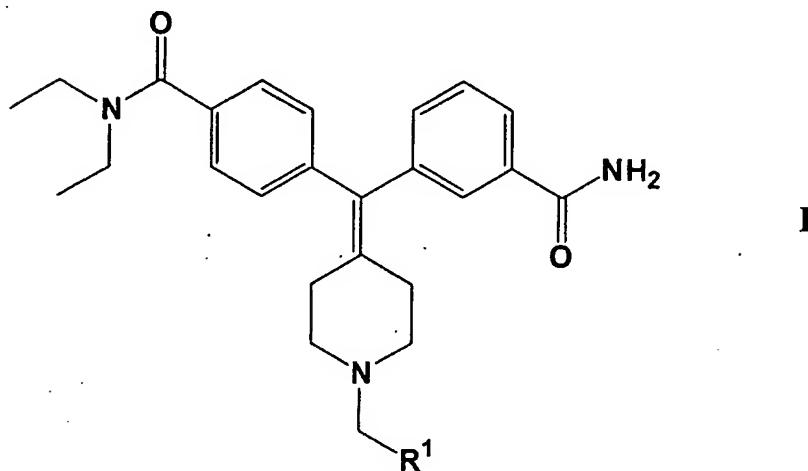
Thus, the problem underlying the present invention was to find new analgesics having improved analgesic effects, but also with an improved side-effect profile over current μ agonists, as well as having improved systemic efficacy.

Analgesics that have been identified and exist in the prior art have many disadvantages in that 25 they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred δ agonist compounds, described within the prior art, show significant convulsive effects when administered systemically.

We have now found that certain compounds not specifically disclosed by, but included within the scope of WO 98/28275, exhibit surprisingly improved δ -agonist properties and in vivo potency.

Outline of the invention

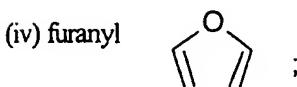
5 The novel compounds according to the present invention are defined by the formula I
wherein



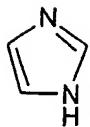
10 R^1 is selected from any one of



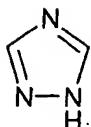
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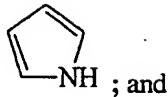
(v) imidazolyl



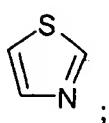
(vi) triazolyl



(vii) pyrrolyl



(viii) thiazolyl



10 where each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents independently selected from straight and branched C_1 - C_6 alkyl, NO_2 , CF_3 , C_1 - C_6 alkoxy, chloro, fluoro, bromo, and iodo. The substitutions on the phenyl ring and on the heteroaromatic ring may take place in any position on said ring systems.

Particularly, novel compounds according to the present invention are defined by the formula

15 I

wherein R^1 is selected from any one of



(i) phenyl



(ii) pyridinyl



(iii) thiienyl

and

20

(iv) furanyl



Within the scope of the invention are also salts and enantiomers of the compounds of the formula I.

When the phenyl ring and the heteroaromatic ring(s) are substituted, the preferred substituents are independently selected from any one of CF_3 , methyl, iodo, bromo, fluoro and chloro.

The novel compounds of the present invention are useful in therapy, especially for the treatment of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety, urinary incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

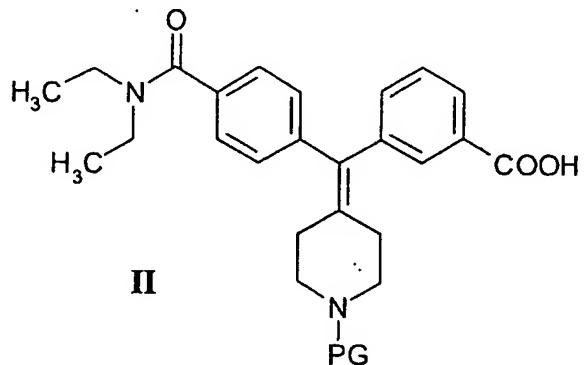
Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the

formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the formula I above, is administered to a patient in need of such treatment.

5 A further aspect of the present invention is intermediates of the general formula II

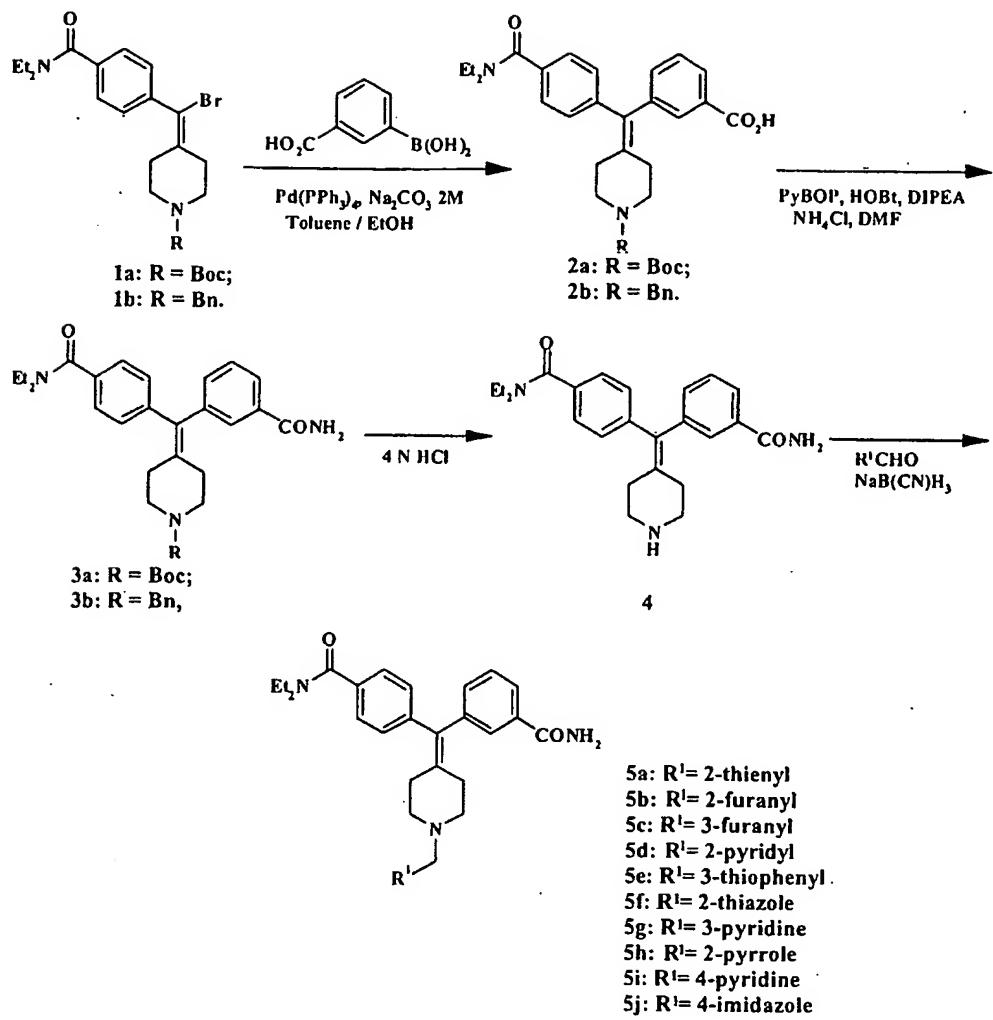


wherein PG is a urethane protecting group such as Boc or CBZ, or a benzyl or substituted benzyl protecting group, such as 2,4-dimethoxybenzyl.

10 Methods of preparation

EXAMPLES

The invention will now be described in more detail by the following Schemes and Examples, which are not to be construed as limiting the invention.



Scheme 1: Synthetic Route to Compounds of the Present Invention

N,N-Diethyl-4-[N-Boc-piperidin-4-ylidene(3-carboxyphenyl)-methyl]-benzamide (2a).

A mixture of 4-[bromo-(4-diethylcarbamoyl-phenyl)-methylene]-piperidine-1-carboxylic acid **5** (451 mg, 1.0 mmol), 3-carboxyphenyl boronic acid (330 mg, 2.0 mmol), 2M Na₂CO₃ (3 mL), and tetrakis(triphenyl phosphine) palladium(0) (25 mg) in toluene (degassed, 10 mL) and ethanol (degassed, 10 mL) was refluxed at 90 °C for 4 hrs under N₂. The reaction mixture was then quenched with aqueous NH₄Cl after cooling down to 0 °C, and extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, and evaporated to give a crude product, which was purified by flash silica gel column to provide the desired compound **2a** (345 mg, 70 %): ¹H NMR (CDCl₃) δ 1.15 (3 H, br m, CH₃CH₂-), 1.23 (3 H, br m, CH₃CH₂-), 1.47 (9 H, s, C(CH₃)₃), 2.31 (2 H, m, piperidine CH-), 2.35 (2 H, m,

piperidine CH-), 3.30 (2 H, br m, CH₃CH₂N-), 3.48 (4 H, m, piperidine CH-), 3.54 (2 H, br m, CH₃CH₂N-), 7.14 (2 H, d, J = 8.0 Hz, ArH), 7.24 (1 H, m, ArH), 7.33 (2 H, d, J = 8.0 Hz, ArH), 7.42 (1 H, t, J = 7.6 Hz, ArH), 7.86 (1 H, s, ArH), 7.97 (1 H, d, J = 7.6 Hz, ArH). IR (NaCl) 2976, 1718, 1691, 1598, 1430, 1233, 1166 cm⁻¹.

5 N,N-Diethyl-4-[1-(benzyl-piperidin-4-ylidene-(3-carboxyphenyl)-methyl]-benzamide (2b).

Method as for 2a using 1b (441 mg, 1.0 mmol) and 3-carboxyphenyl boronic acid (330 mg, 2.0 mmol) provided 2b (325 mg, 67 %): ¹H NMR (CDCl₃) δ 1.11 (3 H, br m, CH₃CH₂-), 1.22 (3 H, br m, CH₃CH₂-), 2.63 (4 H, m, piperidine CH-), 2.90 (4 H, m, piperidine CH-), 3.26 (2 H, br m, CH₃CH₂N-), 3.52 (2 H, br m, CH₃CH₂N-), 4.00 (2 H, s, CH₂N-), 7.11 (2 H, d, J = 8.0 Hz, ArH), 7.16 (1H, m, ArH), 7.30 (6 H, m, ArH), 7.42 (2 H, m, ArH), 7.84 (1 H, s, ArH), 7.96 (1 H, d, J = 7.6 Hz, ArH).

N,N-Diethyl-4-[1-benzylpiperidin-4-ylidene(3-carbamoylphenyl)-methyl]-benzamide (3b).

15 241 mg (0.5 mmol) of N,N-diethyl-4-[piperidin-4-ylidene(3-carboxyphenyl)-methyl]-benzamide (2b), 780 mg (1.5 mmol) of PyBOP, and 200 mg (1.5 mmol) of HOBr were dissolved in 4 mL DMF. 0.58 mL (4 mmol) of DIPEA and 50 mg (10.0 mmol) of NH₄Cl were added successively. After stirred for 0.5 h at room temperature, the reaction mixture was quenched with water and ethyl ether. The white precipitates were collected as the desired product (3b, 152 mg, 63 %): ¹H NMR (CDCl₃) δ 1.10 (3 H, br m, CH₃CH₂-), 1.21 (3 H, br m, CH₃CH₂-), 2.62 (4 H, m, piperidine CH-), 2.89 (4 H, m, piperidine CH-), 3.26 (2 H, br m, CH₃CH₂N-), 3.52 (2 H, br m, CH₃CH₂N-), 4.00 (2 H, s, CH₂N-), 7.11 (2 H, d, J = 8.0 Hz, ArH), 7.16 (1H, m, ArH), 7.30 (6 H, m, ArH), 7.42 (2 H, m, ArH), 7.84 (1 H, s, ArH), 7.96 (1 H, d, J = 7.6 Hz, ArH);
Anal. Calcd. for C₃₁H₃₅N₃O₂ 6.0 HCl: C, 53.16 %; H, 5.90 %; Found: C, 53.07 %; H, 5.54 %.

25 N,N-Diethyl-4-[piperidin-4-ylidene(3-carbamoylphenyl)-methyl]-benzamide (4).

Method as for 3b using 2a (150 mg, 0.30 mmol) provided 3a (105 mg, 70 %): ¹H NMR (CDCl₃) δ 1.14 (3 H, br m, CH₃CH₂-), 1.22 (3 H, br m, CH₃CH₂-), 1.46 (9 H, s, C(CH₃)₃), 2.28 (2 H, m, piperidine CH-), 2.33 (2 H, m, piperidine CH-), 3.30 (2 H, br m, CH₃CH₂N-), 3.46

(4 H, m, piperidine CH-), 3.55 (2 H, br m, CH₃CH₂N-), 7.13 (2 H, d, J = 8.0 Hz, ArH), 7.30 (3 H, m, ArH), 7.39 (1 H, t, J = 7.6 Hz, ArH), 7.61 (1 H, s, ArH), 7.68 (1 H, d, J = 7.6 Hz, ArH).

The above product (3a) was treated with 4.0 M HCl in dioxane (10 mL) at room temperature for 4 h. After evaporation, the residue was dissolved in H₂O (10 mL) and impurities were extracted with ethyl acetate (2 x 20 mL). The aqueous phase was basified with NH₄OH and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄ and evaporated to give 4 in quantitative yield: ¹H NMR (CDCl₃) δ 1.15 (3 H, br m, CH₃CH₂-), 1.23 (3 H, br m, CH₃CH₂-), 1.90 (2 H, br, NH₂), 2.31 (2 H, m, piperidine CH-), 2.34 (2 H, m, piperidine CH-), 2.92 (4 H, m, piperidine CH-), 3.32 (2 H, br m, CH₃CH₂N-), 3.55 (2 H, br m, CH₃CH₂N-), 7.13 (2 H, d, J = 8.0 Hz, ArH), 7.30 (3 H, m, ArH), 7.38 (1 H, t, J = 7.6 Hz, ArH), 7.58 (1 H, s, ArH), 7.66 (1 H, d, J = 7.6 Hz, ArH). IR (NaCl) 3307, 2973, 1668, 1615, 1435, 1383, 1289 cm⁻¹; Anal. Calcd. for C₂₄H₂₉N₃O₂ 2.8 HCl: C, 58.40 %; H, 6.49 %; Found: C, 58.46 %; H, 6.57 %.

N,N-Diethyl-4-[1-(2-thiophene)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5a).

To a mixture of N,N-diethyl-4-[piperidin-4-ylidene(3-carbamoylphenyl)-methyl]-benzamide (4, 196 mg, 0.5 mmol); 2-thiophenecarboxaldehyde (112 mg, 1.0 mmol), acetic acid (0.1 mL) in MeOH (10 mL) was added NaBH₃(CN) (200 mg) in portions. The reaction mixture was stirred for 4 h at room temperature, and then quenched with aqueous NH₄Cl, extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were washed with brine, dried over MgSO₄, and evaporated to give a crude product, which was purified by flash silica gel column to give the desired product (5a, 216 mg, 89 %). ¹H NMR (CDCl₃) δ 1.13 (3 H, br m, CH₃CH₂-), 1.22 (3 H, br m, CH₃CH₂-), 2.36 (2 H, m, piperidine CH-), 2.42 (2 H, m, piperidine CH-), 2.54 (4 H, m, piperidine CH-), 3.26 (2 H, br m, CH₃CH₂N-), 3.52 (2 H, br m, CH₃CH₂N-), 3.76 (2 H, s, CH₂N-), 5.60 (1 H, br, NH), 6.06 (1 H, br, NH), 6.91 (1 H, s, ArH), 6.94 (1 H, m, ArH), 7.12 (2 H, d, J = 8.0 Hz, ArH), 7.26 (1 H, m, ArH), 7.30 (3 H, m, ArH), 7.37 (1 H, t, J = 7.6 Hz, ArH), 7.56 (1 H, s, ArH), 7.64 (1 H, d, J = 7.6 Hz, ArH). IR (NaCl) 3352, 2973, 1668, 1614, 1434, 1290 cm⁻¹; Anal. Calcd. for C₂₉H₃₃N₃O₂S 2.3 HCl: C, 60.95 %; H, 6.23 %; Found: C, 60.96 %; H, 6.42 %.

N,N-Diethyl-4-[1-(2-furfuryl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5b).

Method as for **5a** using **4** (196 mg, 0.5 mmol) and 2-furaldehyde (96 mg, 1.0 mmol) provided **5b** (158 mg, 67 %): ¹H NMR (CDCl₃) δ 1.12 (3 H, br m, CH₃CH₂-), 1.22 (3 H, br m, CH₃CH₂-), 2.41 (4 H, m, piperidine CH-), 2.83 (4 H, m, piperidine CH-), 3.27 (2 H, br m, CH₃CH₂N-), 3.52 (2 H, br m, CH₃CH₂N-), 3.88 (2 H, s, CH₂N-), 6.18 (1 H, br, NH), 6.35 (1 H, m, ArH), 6.42 (1 H, m, ArH), 6.86 (1 H, m, NH), 7.12 (2 H, d, J = 8.0 Hz, ArH), 7.27 (3 H, m, ArH), 7.32 (1 H, m, ArH), 7.41 (1 H, s, ArH), 7.61 (1 H, s, ArH), 7.69 (1 H, d, J = 7.6 Hz, ArH); *Anal. Calcd. for C₂₉H₃₃N₃O₃ 3.0 HCl: C, 59.95 %; H, 6.25 %; Found: C, 59.68 %; H, 5.98 %.*

N,N-Diethyl-4-[1-(3-furfuryl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5c).

Method as for **5a** using **4** (196 mg, 0.5 mmol) and 3-furaldehyde (96 mg, 1.0 mmol) provided **5c** (143 mg, 61 %): ¹H NMR (CDCl₃) δ 1.13 (3 H, br m, CH₃CH₂-), 1.25 (3 H, br m, CH₃CH₂-), 2.42 (4 H, m, piperidine CH-), 2.70 (4 H, m, piperidine CH-), 3.26 (2 H, br m, CH₃CH₂N-), 3.52 (2 H, br m, CH₃CH₂N-), 3.62 (2 H, s, CH₂N-), 5.80 (1 H, br, NH), 6.42 (1 H, br, NH), 6.46 (1 H, s, ArH), 7.12 (2 H, d, J = 8.0 Hz, ArH), 7.28 (3 H, m, ArH), 7.36 (1 H, t, J = 7.6 Hz, ArH), 7.42 (2 H, m, ArH), 7.59 (1 H, s, ArH), 7.66 (1 H, d, J = 7.6 Hz, ArH); *Anal. Calcd. for C₂₉H₃₃N₃O₃ 3.1 HCl: C, 59.58 %; H, 6.22 %; Found: C, 59.44 %; H, 6.45 %.*

N,N-Diethyl-4-[1-(2-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5d).

Method as for **5a** using **4** (196 mg, 0.5 mmol) and 2-pyridinecarboxaldehyde (107 mg, 1.0 mmol) provided **5d** (35 mg, 15 %): ¹H NMR (CDCl₃) δ 1.13 (3 H, br m, CH₃CH₂-), 1.24 (3 H, br m, CH₃CH₂-), 2.38 (2 H, m, piperidine CH-), 2.42 (2 H, m, piperidine CH-), 2.56 (4 H, m, piperidine CH-), 3.26 (2 H, br m, CH₃CH₂N-), 3.54 (2 H, br m, CH₃CH₂N-), 3.68 (2 H, s, CH₂N-), 5.64 (1 H, br, NH), 6.12 (1 H, br, NH), 7.14 (3 H, m, ArH), 7.31 (3 H, m, ArH), 7.35 (1 H, m, ArH), 7.38 (1 H, m, ArH), 7.56 (1 H, s, ArH), 7.65 (2 H, m, ArH), 8.58 (1 H, m, ArH).

N,N-Diethyl-4-[1-(3-thiophene)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-

benzamide (5e).

Method as for **5a** using **4** (196 mg, 0.5 mmol) and 3-thiophenecarboxaldehyde (112 mg, 1.0 mmol) provided **5e** (185 mg, 76 %): ^1H NMR (CDCl_3) δ 1.13 (3 H, br m, CH_3CH_2-), 1.24 (3 H, br m, CH_3CH_2-), 2.46 (4 H, m, piperidine $\text{CH}-$), 2.84 (4 H, m, piperidine $\text{CH}-$), 3.26 (2 H, br m, $\text{CH}_3\text{CH}_2\text{N}-$), 3.52 (2 H, br m, $\text{CH}_3\text{CH}_2\text{N}-$), 3.91 (2 H, s, $\text{CH}_2\text{N}-$), 5.72 (1 H, br, NH), 6.44 (1 H, br, NH), 7.13 (3 H, m, ArH), 7.26 (3 H, m, ArH), 7.36 (3 H, m, ArH), 7.61 (1 H, s, ArH), 7.68 (1 H, d, $J = 7.6$ Hz, ArH); *Anal. Calcd. for* $\text{C}_{29}\text{H}_{33}\text{N}_3\text{O}_2\text{S}$ 2.5 HCl: C, 60.18 %; H, 6.18 %; *Found:* C, 60.16 %; H, 6.49 %.

10 N,N-Diethyl-4-[1-(2-thiazole)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5f).

To a solution of N,N-diethyl-4-[piperidin-4-ylidene(3-carbamoylphenyl)-methyl]-benzamide (**4**, 300 mg, 0.8 mmol) in 1,2-dichloroethane (15 mL) was added 2-thiazole carboxaldehyde (94 μL , 1.1 mmol) and sodium triacetoxyborohydride (228 mg, 1.1 mmol). The reaction mixture was stirred for 20h at room temperature, and then quenched with aqueous NaHCO_3 . The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic phases were dried over MgSO_4 , filtered and evaporated. The crude product was purified by flash chromatography to give product (**5f**) as a yellow foam (234 mg, 63% yield).

The product was dissolved in dichloromethane (5mL) and a solution of HCl in ether (1N, 1.4 mL, 3eq.) was added. After 30 minutes the suspension was concentrated and the solid dried. ^1H NMR (CDCl_3) δ 1.10 (3H, t, $J=7\text{Hz}$, CH_3) ; 1.21 (3H, t, $J=7\text{Hz}$, CH_3) ; 2.64 (4H, br s, CH_2) ; 3.27-3.31 (4H, m, CH_2) ; 3.48-3.53 (2H, m, CH_2) ; 3.67 (2H, br s, CH_2) ; 4.77 (2H, s, NCH_2Ar) ; 7.27 (2H, d, $J=8.5\text{Hz}$, Ar-H) ; 7.33-7.37 (3H, m, Ar-H) ; 7.44 (1H, t, $J=7.5\text{Hz}$, Ar-H) ; 7.68-7.69 (1H, m, Ar-H) ; 7.75-7.78 (2H, m, Ar-H) ; 7.94 (1H, d, $J=3.5\text{Hz}$, Ar-H). *Anal. Calcd. for* $\text{C}_{28}\text{H}_{32}\text{N}_4\text{O}_2\text{S} \times 2.5\text{HCl}$: C, 58.00%; H, 6.00%; N, 9.66%; *Found:* C, 58.00%; H, 5.95%; N, 9.43%.

N,N-Diethyl-4-[1-(3-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5g).

Method as for **5f** using **4** (176 mg, 0.45 mmol) and 3-pyridinecarboxaldehyde (60 μL , 0.6 mmol) provided **5g** (91.5 mg, 42 %): ^1H NMR (CDCl_3) δ 1.09 (3H, t, $J=7\text{Hz}$, CH_3) ; 1.21

(3H, t, $J=7$ Hz, CH_3) ; 2.68-2.75 (4H, m, CH_2) ; 3.26-3.28 (4H, m, CH_2) ; 3.43-3.60 (4H, m, CH_2) ; 4.65 (2H, s, NCH_2Ar) ; 7.27 (2H, d, $J=8.5$ Hz, Ar-H) ; 7.32-7.36 (3H, m, Ar-H) ; 7.43 (1H, t, $J=8$ Hz, Ar-H) ; 7.70-7.71 (1H, m, Ar-H) ; 7.75-7.78 (1H, m, Ar-H) ; 8.19 (1H, dd, $J=6$, 8Hz, Ar-H) ; 8.88 (1H, d, $J=8$ Hz, Ar-H) ; 8.98 (1H, d, $J=6$ Hz, Ar-H) ; 9.21 (1H, s, Ar-H). *Anal.* 5 *Calcd for* $\text{C}_{30}\text{H}_{34}\text{N}_4\text{O}_2 \times 3.1\text{HCl} \times 0.4\text{H}_2\text{O}$: C, 59.77%; H, 6.34%; N, 9.29%; *Found*: C, 59.70%; H, 6.36%; N, 9.17%.

N,N-Diethyl-4-[1-(2-pyrrole)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5h).

Method as for **5f** using **4** (261 mg, 0.7 mmol) and 2-pyrrolecarboxyaldehyde (89 mg, 0.9 mmol) provided **5h** (118.5 mg, 38 %): ^1H NMR (CDCl_3) δ 1.09 (3H, t, $J=7$ Hz, CH_3) ; 1.21 (3H, t, $J=7$ Hz, CH_3) ; 2.46-2.53 (2H, m, CH_2) ; 2.65-2.77 (2H, m, CH_2) ; 2.97-3.04 (2H, m, CH_2) ; 3.26-3.30 (2H, m, CH_2) ; 3.46-3.52 (4H, m, CH_2) ; 4.30 (2H, s, NCH_2Ar) ; 6.33-6.34 (1H, m, Ar-H) ; 6.85-6.86 (1H, m, Ar-H) ; 7.24-7.26 (2H, m, Ar-H) ; 7.30-7.36 (4H, m, Ar-H) ; 7.40-7.45 (1H, m, Ar-H) ; 7.67-7.68 (1H, m, Ar-H) ; 7.75-7.77 (1H, m, Ar-H). *Anal.* *Calcd for* 15 $\text{C}_{29}\text{H}_{34}\text{N}_4\text{O}_2 \times 1.1\text{HCl} \times 1.8\text{H}_2\text{O}$: C, 64.13%; H, 7.18%; N, 10.32%; *Found*: C, 64.26%; H, 7.15%; N, 9.94%.

N,N-Diethyl-4-[1-(4-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5i).

Method as for **5f** using **4** (329 mg, 0.8 mmol) and 4-pyridinecarboxyaldehyde (112 μL , 1.2 mmol) provided **5i** (217 mg, 54 %): ^1H NMR (CDCl_3) δ 1.12 (3H, t, $J=7$ Hz, CH_3) ; 1.24 (3H, t, $J=7$ Hz, CH_3) ; 2.67-2.82 (4H, m, CH_2) ; 3.22-3.34 (4H, m, CH_2) ; 3.49-3.65 (4H, m, CH_2) ; 4.72 (2H, s, NCH_2Ar) ; 7.29 (2H, d, $J=8.5$ Hz, Ar-H) ; 7.33-7.40 (3H, m, Ar-H) ; 7.46 (1H, t, $J=8$ Hz, Ar-H) ; 7.72-7.73 (1H, m, Ar-H) ; 7.78-7.80 (1H, m, Ar-H) ; 8.37 (2H, d, $J=7$ Hz, Ar-H) ; 9.00 (2H, d, $J=7$ Hz, Ar-H).

25 **N,N-Diethyl-4-[1-(4-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide (5j).**

Method as for **5f** using **4** (313 mg, 0.8 mmol) and 4-imidazolecarboxyaldehyde (108 mg, 1.1 mmol) provided **5j** (68.2 mg, 18 %): ^1H NMR (CDCl_3) δ 1.12 (3H, t, $J=7$ Hz, CH_3) ; 1.23 (3H, t, $J=7$ Hz, CH_3) ; 2.63 (2H, t, $J=6$ Hz, CH_2) ; 2.68 (2H, t, $J=6$ Hz, CH_2) ; 3.26-3.36 (6H, m, CH_2)

;3.54 (2H, q, J=7Hz, CH₂) ; 4.45 (2H, s, NCH₂Ar) ; 7.28 (2H, d, J=8Hz, Ar-H) ; 7.32-7.40 (3H, m, Ar-H) ; 7.45 (1H, t, J=8Hz, Ar-H) ; 7.66 (1H, s, Ar-H) ; 7.71 (1H, t, J=2Hz, Ar-H) ; 7.76-7.82 (1H, m, Ar-H) ; 8.61 (1H, s, Ar-H).

5 **Pharmaceutical compositions**

The novel compounds according to the present invention may be administered orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

A preferred route of administration is orally, intravenously or intramuscularly.

10 The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level as the most appropriate for a particular patient.

15 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

20 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

25 For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Salts include, but are not limited to, pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts within the scope of the present invention include: acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, 5 gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclinate. Examples of pharmaceutically unacceptable 10 salts within the scope of the present invention include: hydroiodide, perchlorate, and tetrafluoroborate.

Preferred pharmaceutically acceptable salts are the hydrochlorides, sulfates and bitartrates.

The hydrochloride and sulfate salts are particularly preferred.

The term composition is intended to include the formulation of the active component with 15 encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or 20 water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents 25 as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

BIOLOGICAL EVALUATION

In vitro model

Cell culture

- 10 A. Human 293S cells expressing cloned human μ , δ , and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO₂ in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68; and 600 μ g/ml geneticin.
- 15 B. Mouse and rat brains were weighed and rinsed in ice-cold PBS (containing 2.5mM EDTA, pH 7.4). The brains were homogenized with a polytron for 15 sec (mouse) or 30 sec (rat) in ice-cold lysis buffer (50mM Tris, pH 7.0, 2.5mM EDTA, with phenylmethylsulfonyl fluoride, added just prior use to 0.5MmM from a 0.5M stock in DMSO:ethanol).

Membrane preparation

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 20 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at 1000 g (max) for 10 min at 4 °C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g (max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final 25 pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in dry ice/ethanol and stored at -70 °C until use. The protein concentrations were determined by a modified Lowry assay with sodium dodecyl sulfate.

Binding assays

Membranes were thawed at 37 °C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM MgCl₂, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 m filter, and to which had been 5 freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl were added to iced 12x75 mm polypropylene tubes containing 100 µl of the appropriate radioligand and 100 µl of test compound at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 µM naloxone respectively. The tubes were 10 vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM MgCl₂) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethylenimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep 15 well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 µl MS-20 scintillation fluid/well.

Functional Assays

The agonist activity of the compounds is measured by determining the degree to which the 20 compounds receptor complex activates the binding of GTP to G-proteins to which the receptors are coupled. In the GTP binding assay, GTP[γ]³⁵S is combined with test compounds and membranes from HEK-293S cells expressing the cloned human opioid receptors or from homogenised rat and mouse brain. Agonists stimulate GTP[γ]³⁵S binding in these membranes. The EC₅₀ and E_{max} values 25 of compounds are determined from dose-response curves. Right shifts of the dose response curve by the delta antagonist naltrindole are performed to verify that agonist activity is mediated through delta receptors.

Data analysis

The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test compounds was expressed as percentage of control SB. Values of IC₅₀ and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting

programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prusoff equation. Mean \pm S.E.M. values of IC_{50} , K_i and n_H were reported for ligands tested in at least three displacement curves. Biological data are tabulated on the following pages in Table 1.

5

Table 1: Biological data.

Ex. #	MOLECULAR STRUCTURE	HDELTA (nM)			RAT BRAIN		MOUSE BRAIN	
		IC ₅₀	EC ₅₀	%EMax	EC ₅₀	%EMax	EC ₅₀	%EMax
3b		0.548	0.091	93.775	0.403	178.94	0.539	164.82
5a		0.373	0.158	98.107	0.613	181.01	0.818	170.24
5b		0.282			0.633	149.28		

Receptor saturation experiments

Radioligand K_δ values were determined by performing the binding assays on cell membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_δ (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_δ and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

Determination Of Mechano-Alloodynia Using Von Frey Testing

10 Testing was performed between 08:00 and 16:00h using the method described by Chapman et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar

left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, 5 and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

Testing Protocol

The animals were tested on postoperative day 1 for the FCA-treated group. The 50% 10 withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses 15 in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was 20 interpolated using the formula:

$$50\% \text{ g threshold} = 10^{(X_f + k\delta)} / 10,000$$

where X_f = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

25 Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\% \text{MPE} = \frac{\text{Drug treated threshold (g)} - \text{allodynia threshold (g)} \times 100}{\text{Control threshold (g)} - \text{allodynia threshold (g)}}$$

Administration of Test Substance

Rats were injected (subcutaneously, intraperitoneally, intravenously or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

5 Writhing Test

Acetic acid will bring abdominal contractions when administered intraperitoneally in mice. These will then extend their body in a typical pattern. When analgesic drugs are administered, this described movement is less frequently observed and the drug selected as a potential good candidate.

A complete and typical Writhing reflex is considered only when the following elements are 10 present: the animal is not in movement; the lower back is slightly depressed; the plantar aspect of *both* paws is observable. In this assay, compounds of the present invention demonstrate significant inhibition of writhing responses after oral dosing of 1-100 μ mol/kg.

(i) Solutions preparation

Acetic acid (AcOH): 120 μ L of Acetic Acid is added to 19.88 ml of distilled water in 15 order to obtain a final volume of 20 ml with a final concentration of 0.6% AcOH. The solution is then mixed (vortex) and ready for injection.

Compound (drug): Each compound is prepared and dissolved in the most suitable vehicle according to standard procedures.

(ii) Solutions administration

20 The compound (drug) is administered orally, intraperitoneally (i.p.), subcutaneously (s.c.) or intravenously (i.v.) at 10 ml/kg (considering the average mice body weight) 20, 30 or 40 minutes (according to the class of compound and its characteristics) prior to testing. When the compound is delivered centrally: Intraventricularly (i.c.v.) or intrathecally (i.t.) a volume of 5 μ L is administered.

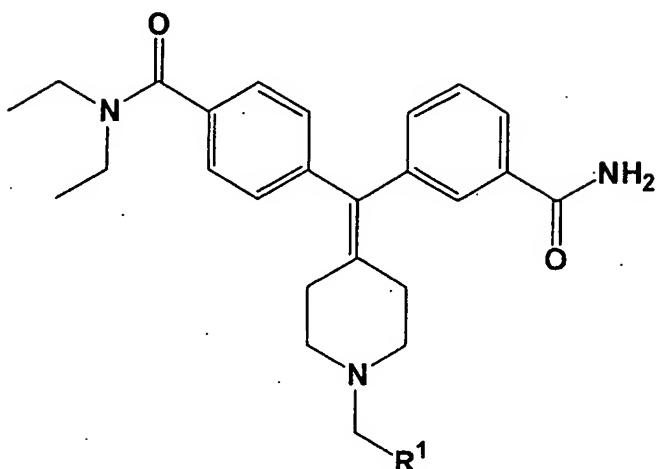
25 The AcOH is administered intraperitoneally (i.p.) in two sites at 10 ml/kg (considering the average mice body weight) immediately prior to testing.

(iii) Testing

The animal (mouse) is observed for a period of 20 minutes and the number of occasions (Writhing reflex) noted and compiled at the end of the experiment. Mice are kept in individual "shoe box" cages with contact bedding. A total of 4 mice are usually observed at the same time: one control and three doses of drug.

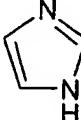
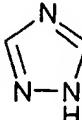
CLAIMS

1. A compound of the formula I



5

wherein

R¹ is selected from any one of10 (i) phenyl (ii) pyridinyl 15 (iii) thiienyl (iv) furanyl 20 (v) imidazolyl (vi) triazolyl 

(vii) pyrrolyl  ; and

(viii) thiazolyl  ;

5 where each R^1 phenyl ring and R^1 heteroaromatic ring may independently be further substituted by 1, 2 or 3 substituents independently selected from straight and branched C_1 - C_6 alkyl, NO_2 , CF_3 , C_1 - C_6 alkoxy, chloro, fluoro, bromo, and iodo; as well as salts thereof.

10 2. A compound according to claim 1 wherein R^1 is selected from any one of

(i) phenyl  ;

(ii) pyridinyl  ;

(iii) thiienyl  ; and

(iv) furanyl  ;

20

3. A compound according to claim 1, wherein each R^1 phenyl ring and R^1 heteroaromatic ring may optionally and independently be further substituted by 1, 2 or 3 substituents independently selected from methyl, CF_3 , chloro, fluoro, bromo, and iodo.

25

4. A compound according to claim 1, selected from any one of

N,N-Diethyl-4-[piperidin-4-ylidene(3-carbamoylphenyl)-methyl]-benzamide;

N,N-Diethyl-4-[1-(2-thiophene)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(2-furfuryl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(3-furfuryl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
5 N,N-Diethyl-4-[1-(2-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(3-thiophene)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(2-thiazole)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
10 N,N-Diethyl-4-[1-(3-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(2-pyrole)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
N,N-Diethyl-4-[1-(4-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide;
and
N,N-Diethyl-4-[1-(4-pyridine)methyl-piperidin-4-ylidene-(3-carbamoylphenyl)-methyl]-benzamide.

15 5. A compound according to Claim 1, in form of its hydrochloride, dihydrochloride, sulfate, tartrate, difluoroacetate or citrate salts.

6. A compound according to any one of claims 1-5 for use in therapy.

20 7. A compound according to claim 6, wherein the therapy is pain management.

8. A compound according to claim 6, wherein the therapy is directed towards gastrointestinal disorders.

25 9. A compound according to claim 6, wherein the therapy is directed towards spinal injuries.

10. A compound according to claim 6, wherein the therapy is directed to disorders of the sympathetic nervous system.

30 11. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of pain.

12. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.
13. Use of a compound according to formula I of claim 1 for the manufacture of a medicament for use in the treatment of spinal injuries.
14. A pharmaceutical composition comprising a compound of the formula I according to claim 1 as an active ingredient, together with a pharmaceutically acceptable carrier.
15. A method for the treatment of pain, whereby an effective amount of a compound of the formula I according to claim 1 is administered to a subject in need of pain management.
16. A method for the treatment of gastrointestinal disorders, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said gastrointestinal disorder.
17. A method for the treatment of spinal injuries, whereby an effective amount of a compound of the formula I according to claim 1, is administered to a subject suffering from said spinal injury.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/01804

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/70, C07D 401/06, C07D 407/06, C07D 409/06, C07D 417/06,
A61K 31/4523, A61K 31/445, A61P 25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9828275 A1 (ASTRA PHARMA INC.), 2 July 1998 (02.07.98), the claims, esp. claims 1-3, 11-14 and claim 4, page 112 --	1-17
P, X	WO 0174804 A1 (ASTRAZENECA AB), 11 October 2001 (11.10.01) -- -----	1-17

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/>	See patent family annex.
*	Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier application or patent but published on or after the international filing date	"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2003	30-01-2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SEO2/01804**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **15-17**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/01804

Claims 15-17 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/01804

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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